Rheumatol Int (2015) 35:289–294
DOI 10.1007/s00296-014-3097-9

SHORT COMMUNICATION

Frequent involvement of central nervous system in primary Sjögren syndrome

Isabel Moreira · Filipa Teixeira · Ana Martins Silva · Carlos Vasconcelos · Fátima Farinha · Ernestina Santos

Received: 25 February 2014 / Accepted: 15 July 2014 / Published online: 24 July 2014

Abstract Primary Sjögren syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the salivary and tear glands, and autoantibody secretion, in the absence of other systemic autoimmune disorder. Among autoimmune diseases, it is a relatively common disease, but the burden of central nervous system (CNS) involvement is controversial. This retrospective study evaluates the prevalence, clinical patterns and outcomes of CNS involvement in a cohort of patients with primary Sjögren syndrome. We evaluated 93 patients with pSS diagnosed according to American-European Consensus Group criteria. Fourteen patients (15.1 %) had CNS involvement. All were women with an average age of onset of the disease of 42.1 ± 14.7 years (average ± SD) and an average age of onset of neurological involvement of 47.29 ± 16 years. Three had parkinsonian syndrome, two epilepsy, two motor and sensory deficits, two headache with brain magnetic resonance abnormalities, two neuromyelitis optica, two chronic progressive myelitis and one aseptic meningitis. Neurological involvement preceded Sjögren syndrome diagnosis in nine of the patients (64 %), and neurological outcome was good in 11 patients (78.6 %). Central nervous involvement was not as rare as expected, and the frequency was similar to the frequency of peripheral nervous system involvement. In half of the patients, this was the first symptom of the disease, emphasizing the importance of considering this diagnosis, especially in young female with neurological symptoms without other evident cause.

Keywords Sjögren syndrome · Sicca syndrome · Autoimmune diseases · Central nervous system · Neuroimmune process · Keratoconjunctivitis sicca

I. Moreira (✉) · A. Martins Silva · E. Santos
Neurology Department, Hospital Santo António, Centro Hospitalar do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal
e-mail: isabelpmoreira@gmail.com

F. Teixeira
Rheumatology Department, Unidade Local de Saude do Alto Minho, Largo Conde de Bertiandos, 4990-041 Ponte de Lima, Portugal

C. Vasconcelos · F. Farinha
Clinical Immunology Unit, Hospital Santo António, Centro Hospitalar do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal

Introduction

Sjögren syndrome is a systemic autoimmune disease characterized mainly by lymphocytic infiltrates of salivary and tear glands, leading to oral and ocular dryness and by autoantibody secretion [1]. It can be present alone, which is known as primary Sjögren syndrome (pSS), or with other systemic autoimmune disorders, known as secondary Sjögren syndrome [1]. pSS prevalence in general adult population is 0.1–0.6 %, making it the second most frequent systemic autoimmune disease after rheumatoid arthritis. It is more frequent in women (with a female to male ratio of 9:1) and has an age peak in mid-50's [2].

Peripheral nervous system (PNS) involvement is well documented, affecting 10–20 % of pSS patients [3]. Central nervous system (CNS) involvement is described to be less frequent, but real prevalence is unknown. The objective of this study was to describe the prevalence, clinical patterns and outcomes of CNS involvement in pSS patients followed in the Clinical Immunology Unit in our center.

Patients and methods

We performed a retrospective study, evaluating all patients with pSS (according to the revised version of the European criteria proposed by the American-European Consensus Group in 2002 [4]) registered in the Clinical Immunology Unit database of our center.

We collected the following data from the medical records: age of disease onset, age at diagnosis, age at the first neurological manifestation and the duration of the disease (calculated from disease onset to January 2012), complaints of oral and ocular dryness, constitutional symptoms, Raynaud phenomenon, vasculitis, joints, skin, pulmonary, kidney, gastrointestinal and endocrine involvement. Headache was included if associated with magnetic resonance imaging (MRI) abnormalities. Cognitive complaints were included if they had criteria for dementia, according to clinical and neuropsychological data. Other complains such as mild cognitive dysfunction, depression and anxiety were excluded. Neurological outcome relied on Modified Oxford Handicap Scale (MOHS). All patients with neurological symptoms were evaluated by a neurologist, and neurological manifestations were only attributed to pSS after excluding other causes.

We recorded in all patients: serum immunoglobulin G, complement C3 and C4, cryoglobulins, rheumatoid factor, anti-nuclear, anti-SS-A, anti-SS-B and anti-phospholipid antibodies. Anti-aquaporin 4 (anti-AQP4) and NMDAr antibodies, MRI, electroencephalogram (EEG) and cerebrospinal fluid (CSF) analysis were performed in some patients depending on each clinical case. Brain MRIs were considered abnormal if had white matter T2-hyperintense small lesions located in the subcortical and/or periventricular regions, without gadolinium enhancement.

The data of pSS patients with and without CNS involvement were compared using SPSS 17.1 software. We used Fisher's exact tests and student T tests to categorical and continuous variables, respectively. Statistical significance assumed was $p < 0.05$ within a 95 % confidence interval.

Results

We enrolled 93 pSS patients. The data from patients with and without CNS involvement and the comparison between them are presented in Table 1.

Neurological involvement was present in 26 patients with pSS (28 % of the 93 pSS patients): 12 (12.9 %) had only PNS involvement, 13 (14 %) had only CNS disorders, and one had PNS and CNS involvement. The ratio between women and men was 30:1, respectively, from all patients. Those with neurological involvement were all women.

The age at onset of pSS was 41.3 ± 11.7 years (average ± SD) considering the 93 patients and was 41.2 ± 11.15 years in the patients without CNS involvement and 42.1 ± 14.7 years in those with CNS involvement. The age at diagnosis of pSS was 47.2 ± 13 years in pSS patients, 47.5 ± 11.57 years in patients without CNS involvement and 45.4 ± 15.6 in patients with CNS involvement. The average age of CNS first manifestation was 47.29 ± 16 years (between 19 and 66 years). Neurological manifestations preceded pSS diagnosis in nine of the patients with CNS involvement (64 % of the 14 patients with CNS involvement) and in 15 of the patients with neurological involvement (58 % of the 26 patients with neurological involvement), but only two patients did not have sicca symptoms at the onset of neurological manifestation. In these parameters, there was not statistically significant difference between those without and with CNS involvement.

Constitutional symptoms and lung involvement were significantly more frequent in those with CNS involvement than in those without CNS involvement ($p = 0.001$ and $p = 0.027$, respectively). Arthritis/joint symptoms were significantly more frequent in those without CNS involvement ($p = 0.015$). The other parameters did not have statistically significant difference.

CNS syndromes

The clinical syndromes presented by the patients with CNS involvement are described in the Table 2.

Three patients had movement disorders: one with atypical parkinsonian syndrome beginning at 40 years with symmetric akinetic-rigid syndrome and postural instability, without significant tremor; the second patient beginning at 65 years with asymmetric tremor and bradykinesia, resembling idiopathic Parkinson's disease; and the third patient with dementia and visual hallucinations at 62 years and 6 months later parkinsonian syndrome with rigidity, bradykinesia and asymmetric tremor. Brain MRI showed multiple subcortical and deep white matter lesions. CSF had oligoclonal bands unmatched in serum. None improved with L-dopa.

Two patients had epilepsy with complex partial seizures, starting at 23 and 66 years, 1 year before the beginning of the sicca symptoms. Brain MRI showed a frontal subcortical white matter lesion in the first patient and multiple periventricular white matter, semioval, thalamus and cerebellar lesions in the second. EEGs had paroxysmal anterior and lateral activity, bilaterally, with generalized paroxysmal activity with spikes and waves during seizures. CSF was normal. Anti-NMDAr and anti-VGKC antibodies were negative. The first patient is on valproic acid and zonizamide with 1–3 seizures/day; the other is on valproic acid and clobazam without seizures.

Two patients had motor and sensory deficits. In the first patient, it happened at 40 years old with sudden onset of

Table 1 Results from patients with and without CNS involvement

	All patients	Patients without CNS involvement	Patients with CNS involvement	*p* value
Number	93	79	14	
Ratio women: men	90:3	76:3	14:0	
Age at onset of symptoms				
Median (SD)	41.3 (±11.7)	41.2 (±11.2)	42.1 (±14.7)	0.992
Variance	13–67	13–67	19–67	
Age at diagnosis				
Median (SD)	47.2 (±13)	47.5 (±11.6)	45.4 (±15.6)	0.389
Variance	20–78	21–78	20–69	
Duration of the disease (year)				
Median (SD)	13.8 (±8.4)	14.2 (±8.4)	11.1 (±8.3)	0.146
Variance	1–45	2–45	1–31	
Ocular symptoms	88	76	12	0.108
Oral symptoms	91	78	13	0.280
Constitutional symptoms	30	20	10	**0.001**
Musculo-skeletic symptoms	57	53	4	**0.015**
Raynaud phenomenon	32	27	5	1.000
Skin alterations	13	11	2	1.000
Lung involvement	9	5	4	**0.027**
Gastrointestinal involvement	21	18	3	1.000
Kidney involvement	8	6	2	0.351
Endocrine alterations	17	16	1	0.453
Vasculitis	3	1	2	0.580
Headache	12	7	5	0.151
Increased serum immunoglobulin G	23	15	8	0.752
Decreased complement C3	16	16	0	0.118
Decreased complement C4	10	10	0	0.350
Presence of anti-SS-A antibody	86	72	14	0.589
Presence of anti-SS-B antibody	49	45	4	0.078
Presence of rheumatoid factor	56	51	5	0.073
Presence of anti-nuclear antibody	91	77	14	1.000
Anti-phospholipid antibodies	11	7	4	1.000
Presence of cryoglobulins	1	0	1	1.000

Bold values indicate statistically significant difference between the two groups

Table 2 Central neurological syndromes found in our cohort of pSS patients

Central neurological syndromes	Number of patients
Movement disorders (parkinsonian syndrome)	3
Epilepsy	2
Motor and/or sensory deficits	2
Headaches with magnetic resonance abnormalities	2
Neuromyelitis optica	2
Chronic progressive myelitis	2
Isolated	1
With dementia	1
Aseptic meningitis	1

left hemiparesis and dysesthesia. Brain MRI was normal. She recovered in 2 months. The second patient started at 64 years old with tetraparesis and brisk reflexes and had multiple hyperintense T2 lesions on basal ganglia, corpus callosum and pons on brain MRI.

Two patients had migraine with aura (one had visual aura and the other had visual, sensory and dysphasic aura) that started at 26 and 54 years old, respectively. Both had punctiform periventricular white matter lesions on brain MRI. The first was controlled with topiramate and the second with amitriptyline.

Two patients had neuromyelitis optica (NMO) beginning at 19 and 52 years old. Both had consecutive optic neuritis, tetraparesis with pyramidal signs and posterior column

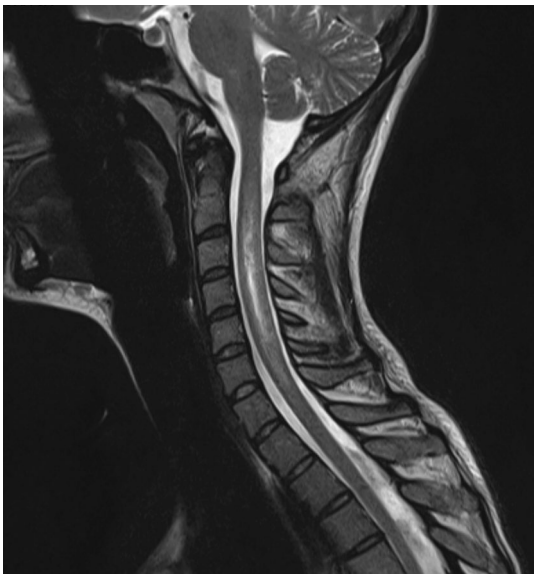

Fig. 1 Centro-medular lesion from C2 to C5 in a patient with neuromyelitis optica

syndrome. Both had primary biliary cirrhosis. Spinal cord MRI showed centro-medular lesion from C2 to C5 in the first patient (Fig. 1) and from C2 to C7 in the second. Brain MRIs were normal. Anti-AQP4 antibodies were positive in both. They were treated with steroids with good response.

Two patients had chronic progressive myelitis with spastic paraparesis and urinary complaints. One started with difficulty in walking at 56 years old and worsened progressively, then developed dementia and died 9 years later. The other began at 53 years old with progressive spastic paraparesis. Brain MRIs showed multiple subcortical and posterior, small, confluent white matter lesions and on the first also cortico–subcortical diffuse atrophy. Spinal cord MRIs were normal.

One patient had aseptic meningitis at 42 years old, presented with diplopia, headache and nucal rigidity. CSF showed 382 leukocytes/μL (55 % polymorphonuclear), increased protein level (1.33 g/L) and no intrathecal immunoglobulin synthesis. Brain MRI was normal. She was treated with steroids with complete resolution of symptoms and CSF changes.

Neurological outcome was good in 11 of the 14 patients. The patient with parkinsonian syndrome and dementia had MOHS 3, the one with chronic progressive myelitis had MOHS 4 and the one with chronic progressive myelitis and dementia died.

Discussion

Before 2002, the criteria used to define pSS were heterogeneous. We compared our study only with those that used the criteria proposed by the American-European Consensus Group in 2002 (Table 3).

Table 3 Studies that evaluated the neurological involvement in pSS patients according the American-European Consensus Group criteria of 2002

Autor/Year/Country	*N*	PNS/CNS	PNS	CNS
Teixeira et al./2012/Portugal [5]	89	22	11	11
Gono et al./2011/Japan [6]	32	20 (62.5 %)	17	6 (19 %)
Massara et al./2010/Italy [7]	424	–	–	25 (5.8 %)
Ramos-Casals/2008/Spain [8]	1,010	–	110 (11 %)	21 (2 %)
Baldini et al./2005/Italy [9]	250	20	20	0 (0 %)
Delalande et al./2004/France [4]	82	82	52 (62 %)	56 (68 %)
Sequeira et al./2004/Portugal [10]	74	24	19 (25.6 %)	5 (6.8 %)
Garcia-Carrasco et al./2003/Spain [11]	400	38	34	4 (1 %)

N number of patients, *PNS/CNS* patients with involvement of peripheral nervous system and central nervous system, *PNS* patients with involvement of peripheral nervous system, *CNS* patients with involvement of central nervous system

In our study, CNS involvement frequency (15 %) is similar to the frequency found in most of the series (0–19 %). Although most of them reported more frequent PNS involvement then CNS involvement, we found a similar frequency in these two groups. This has also been described in one of the largest series that used the same methods as in our study [3].

Although all patients with neurological involvement were women, CNS involvement has been already described in men [3, 7]. Neurological involvement has been described to precede the diagnosis of pSS in 25–81 % of patients [3, 6, 7]. In our study, this happened in 64 % of the patients with CNS involvement and in 58 % of the patients with neurological involvement.

The association between CNS involvement and lung/musculoskeletal involvement was already reported [7], but the association with constitutional symptoms has never been reported. The importance of these findings is still uncertain.

Although the pathophysiology of CNS involvement in pSS is unknown, we believe the cases presented were not casual associations. For example, parkinsonian syndromes had characteristics atypical for a degenerative cause—Parkinson disease, including a poor response to levodopa treatment. All patients with headache included in this study had white matter lesions on MRI consistent with CNS

involvement of pSS. In all cases, extensive investigation work-up was performed excluding other causes for the symptoms.

It seems that it exist more than one mechanism for CNS involvement. Acute focal symptoms, as we described, can mimic stroke, suggesting an ischemic mechanism. However, the recent discovery of anti-AQP4 showed an overlap between pSS and NMO suggesting a vasculitic process [12].

It has been suggested that anti-AQP4 plays a pathogenic role: aquaporin-4 expression is lost in NMO lesions, titters of anti-AQP4 appear to correlate with the disease activity [8, 13], and autopsy cases of NMO spinal cord lesions have revealed immunoglobulin and complement deposits in the endothelial cell wall [12]; on the other hand, it has been suggested common targets between the salivary glands and the CNS, possibly involving protein sequence overlap between aquaporin-4 (predominantly expressed in spinal cord and optic nerves) and aquaporin-5 (predominantly expressed in salivary tissue) [14, 15]. According to the current knowledge, it is fundamental to test for anti-AQP4 in pSS patients with a neuromyelitis optica phenotype, as those with longitudinally extensive transverse myelitis.

Regarding parkinsonian syndrome, there are some reports already. More frequently, they are atypical parkinsonian syndromes with symmetric akinetic-rigid syndrome and postural instability, without prominent tremor. In our study, only one of the patients had these characteristics. As have been reported none responded to L-dopa, but they had a relatively slow progression. One developed subcortical dementia which was rarely described. None had progressive supranuclear palsy, multisystem atrophy or corticobasal degeneration hallmarks. The association between pSS and parkinsonian syndromes is not well understood, but our patients had white matter MRI lesions, and although a poor response to L-dopa, they had a slowly progression. This is not typical for Parkinson's disease and has been described in the parkinsonian syndromes associated with pSS. Some of those patients had white matter lesions similar to those in multiple sclerosis, being hypothesized that they reflect the action of an antibody directed against myelin constituents; others resembled chronic hypertension lesions leading us to think of a small vessel vasculopathy. There are cases with normal MRIs which could result from autoantibodies against basal ganglia [14]. The two patients with dementia had a subcortical dysfunction as has been described [3].

Epilepsy had been described in pSS, but is not well characterized. In a previous case series of 82 patients with pSS with neurological involvement, seven patients had seizures: four had partial seizures and three had generalized seizures [3]. In our study, there were two patients with epilepsy, both with complex partial seizures and EEGs compatible with the symptoms. Pathophysiology mechanism is unknown, and nevertheless, our patients had multiple MRI T2 lesions, none were cortical.

Aseptic meningitis origin is also unknown. Hypersensitivity to some agents or an antibody reaction to meningeal cells had been proposed [15].

Conclusion

Our study shows the great heterogeneity of CNS involvement in pSS patients. CNS involvement was as frequent as PNS involvement. CNS complications presented in more than half of the patients before pSS diagnosis, being in these a diagnostic challenge and emphasizing the need of systematical pSS screening in young female patients with neurological symptoms.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Tzioufas AG, Mitsias DI, Moutsopoulos HM (2008) Sjögren's syndrome. In: Hochberg MC, Silman AJ, Smolen JS et al (eds) Rheumatology. Elsevier, Philadelphia, pp 1348–1349
2. Mavragani CP, Moutsopoulos HM (2010) The geoepidemiology of Sjögren's syndrome. Autoimmun Rev 9(5):A305–A310
3. Delalande S, de Seze J, Fauchais AL et al (2004) Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 83(5):280–291
4. Vitali C, Bombardieri S, Jonsson R et al (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61(6):554–558
5. Teixeira F, Moreira I, Silva A et al (2013) Neurological involvement in primary Sjögren's syndrome. Acta Reumatol Port 38(1):29–36
6. Gono T, Kawaguchi Y, Katsumata Y et al (2011) Clinical manifestations of neurological involvement in primary Sjogren's syndrome. Clin Rheumatol 30(4):485–490
7. Massara A, Bonazza S, Castellino G et al (2010) Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable—clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology (Oxford) 49(8):1540–1549
8. Ramos-Casals M, Solans R, Rosas J et al (2008) Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore) 87(4):210–219
9. Baldini C, Tavoni A, Merlini G et al (2005) Primary Sjogren's syndrome: clinical and serological feature of a single centre. Reumatismo 57(4):256–261
10. Muñoz Mda G, Castelão WC, Saraiva FM et al (2004) Primary Sjögren's syndrome: exocrine and non-exocrine manifestations. Rev Bras Reumatol 44(2):129–138
11. García-Carrasco M, Ramos-Casals M, Rosas J et al (2002) Primary Sjogren Syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 81(4):270–280

12. Dalakas MC (2006) B cells in the pathophysiology of autoimmune neurological disorders: a credible therapeutic target. Pharmacol Ther 112(1):57–70
13. Jarius S, Aboul-Enein F, Waters P et al (2008) Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. Brain 131(Pt. 11):3072–3080
14. Walker RH, Spiera H, Brin MF et al (1999) Parkinsonism associated with Sjögren's syndrome: three cases and a review of the literature. Mov Disord 14(2):262–268
15. Ishida K, Uchihara T, Mizusawa H (2007) Recurrent aseptic meningitis: a new CSF complication of Sjogren's syndrome. J Neurol 254(6):806–807